ΣΠΑΝΙΑ ΕΚΔΗΛΩΣΗ ΣΤΕΛΕΧΙΑΙΑΣ ΕΓΚΕΦΑΛΙΤΙΔΑΣ ΜΕ ΑΥΤΟΜΑΤΗ ΥΦΕΣΗ ΣΕ ΑΣΘΕΝΗ ΜΕ ΑΝΤΙΣΩΜΑΤΑ ΕΝΑΝΤΙ ΤΟΥ ΥΠΟΔΟΧΕΑ ΤΗΣ ΓΛΥΚΙΝΗΣ

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Περίληψη
Ασθενής 67 ετών με ιστορικό σακχαρώδους διαβήτη τύπου ΙΙ προσήλθε λόγω επιληπτικών κρίσεων και πρόσφατης οξείας εγκατάστασης ψυχωσικών εκδηλώσεων. Κατά τη διάρκεια της νοσηλείας του παρατηρήθηκαν επώδυνοι μυϊκοί σπασμοί μυών των άνω άκρων και του θωρακικού τοιχώματος. Στη μαγνητική τομογραφία εγκεφάλου απεικονίστηκε διάχυτη βλάβη στο κεντρικό τμήμα της γέφυρας και των εγκεφαλικών σκελών, με αυξημένο σήμα στις T2/FLAIR ακολουθίες, περιορισμό της διάχυσης (στην ακολουθία DWI), παρουσία μικροαιμορραγιών (στην ακολουθία SWI) και σημεία με σκιαγραφική ενίσχυση. Διενεργήθηκε εκτενής εργαστηριακός και απεικονιστικός διαγνωστικός έλεγχος για ρευματολογικά, λοιμώδη και νεοπλασματικά νοσήματα, ο οποίος ήταν αρνητικός ενώ δεν παρατηρήθηκαν ηλεκτρολυτικές διαταραχές. Ο ασθενής παρουσίασε αυτόματη κλινική βελτίωση χωρίς να λάβει ειδική θεραπεία, πριν ακόμα ολοκληρωθεί ο έλεγχος για αυτοάνοσα νοσήματα. Στον ορό του ασθενούς ανευρέθη αυξημένος τίτλος αντισωμάτων έναντι των υποδοχέων της γλυκίνης (GlyR-Abs), οδηγώντας στη διάγνωση της στελεχιαίας εγκεφαλίτιδας, ενώ ο έλεγχος στο εγκεφαλονωτιαίο υγρό ήταν αρνητικός. Η παρούσα περιγραφή περιστατικού αναδεικνύει τα απεικονιστικά ευρήματα σε ασθενή με στελεχιαία εγκεφαλίτιδα, θετικά αντισώματα έναντι υποδοχέων γλυκίνης και αυτόματη ύφεση/υποχώρηση της συμπτωματολογίας.

Λέξεις Κλειδιά: Στελεχιαία Εγκεφαλίτιδα, Μαγνητική τομογραφία εγκεφάλου, Αντισώματα έναντι των υποδοχέων της γλυκίνης

AN UNCOMMON CAUSE OF BRAINSTEM ENCEPHALITIS WITH SPONTANEOUS REMISSION: ANTI-GLYCINE RECEPTOR ANTIBODY ENCEPHALITIS.

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ABSTRACT
A 67-year-old man with diabetes mellitus presented due to epileptic seizures and acute psychosis. During hospitalization painful spasms of upper-limb- and thoracic-muscles were developed. Diffuse T2/FLAIR-hyperintense lesion in central pons and cerebral-peducles with diffusion-restriction, microhemorrhages

ΕΛΛΗΝΙΚΗ ΝΕΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ

and gadolinium enhancement was depicted in brain-MRI. Electrolyte levels were within normal range and further diagnostic work-up, including rheumatic/infectious/neoplastic diseases was negative. The patient showed spontaneous clinical improvement without specific treatment, before the screening for autoimmune diseases was complete. GlyR-Abs were positive only in serum, leading to the diagnosis of brainstem-encephalitis. This case highlights the radiological findings of brainstem-encephalitis with positive GlyR-Abs and spontaneous remission.

Key words: Brainstem Encephalitis, MRI, Glycine Receptor Antibody

CASE PRESENTATION

A 67-year-old man presented to our Emergency Department due to epileptic seizure and acute psychosis; myalgia and subfebrile temperature were also reported during the past week. His medical history included diabetes mellitus type II. In the postictal period neurological examination revealed right hemiparesis, dysarthria and bilateral pyramidal signs. During hospitalization the patient developed painful spasms of upper-limb- and thorax-muscles, with spontaneous remission.

Brain-MRI demonstrated diffuse T2/FLAIR-hyperintense lesion in central pons and cerebral-peduncles with partial diffusion-restriction and microhemorrhages (Figure 1: Panels A-F). MRI-Angiography, including vessel-wall sequences did not show any signs of vascular stenosis or vasculitis and MRI-Spectroscopy – findings were not indicative of malignancy. Electroencephalography showed mild diffuse abnormal activity, without epileptic discharges.

Electrolyte levels were normal and the cerebrospinal-fluid (CSF)– analysis revealed mild pleocytosis (24 cells) with normal protein and glucose levels. There were no oligoclonal bands and the cytological analysis of CSF did not reveal any malignancy.

Quantiferon test and CSF-PCR analysis for Mycobacterium Tuberculosis, Herpes-Simplex-Virus I/II, Cytomegalovirus, Varizella-Zoster-Virus, Epstein-Barr-Virus, Enterovirus and Cryptococcus were negative. Results of serological tests including human immunodeficiency virus antibody/antigen, Venereal Disease Research Laboratory (VDRL), Coxiella burnetii, Leptospira, Borrelia and Brucella antibodies were also negative. Rheumatologic workup including anticardiolipin/ b2-glycoprotein antibodies, lupus anticoagulant, antinuclear antibodies, antineutrophil cytoplasmic antibody, C3 and C4 complement levels and serum angiotensin converting enzyme revealed unremarkable results. The screening for neoplastic diseases, including whole-body CT and FDG-PET CT, was unremarkable and the results from the protein electrophoresis were within normal range.

After about 15 days of symptomatic onset the patient showed a spontaneous clinical improvement without specific treatment. Later and after the clinical

Figure 1 *Radiologic Findings in GlyR-Abs Brainstem Encephalitis*

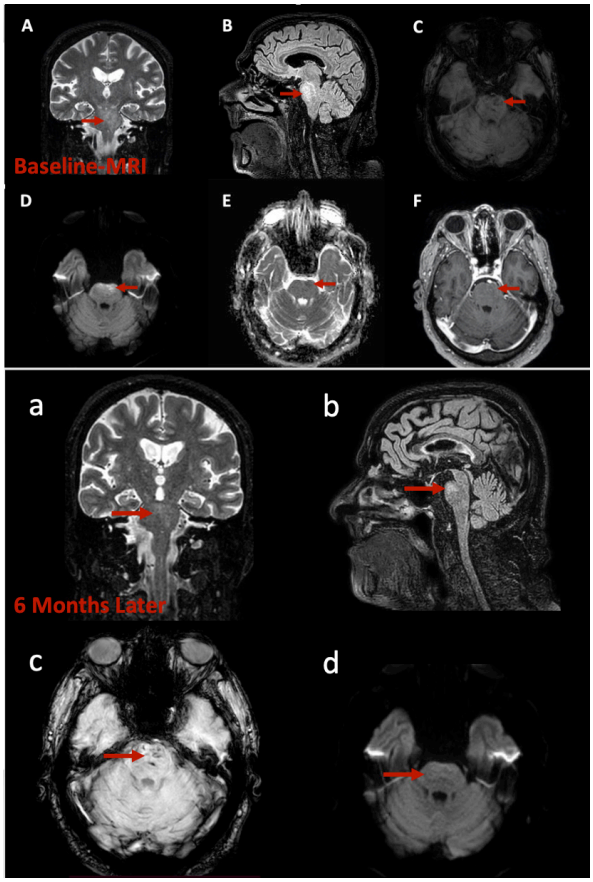

Figure - Legend

Baseline-MRI:

T2-weighted (Panel A) and Fluid-Attenuated Inversion Recovery Sequences (Panel B) showed hyperintense lesion in the pons. Susceptibility-Weighted Imaging depicted microbleeds in brainstem (Panel C). Partial Diffusion Restriction was documented in the pons(Panel D & E). Central located scarce gadolinium enhancement was also present (Panel F).

Follow-up MRI, 6 months later:

T2-weighted (Panel a) and Fluid-Attenuated Inversion Recovery Sequences (Panel b) showed partial remission of the lesion in pons. Microbleeds in brainstem, depicted in Susceptibility Weighted Imaging remain without remarkable change (Panel c). Diffusion-Weighted-Image shows no restriction (Panel d).

improvement the results of the diagnostic work-up revealed positive Glycine-Receptor-Antibodies in serum (GlyR-Abs, Titer:1/100) and negative in CSF. Other antibodies, including GAD, VGKC, anti-AQP4, anti-MOG, amphiphysin, CV2, Hu, PNMA2, Recoverin, Ri, SOX1, Yo, zic4, Tr, Titin, anti-CASPR2, anti-LGI1, anti-NMDAR, anti-AMPAR1,2, anti-GABAbR, anti-mGluR5, anti-DPPX, anti-GQ1b were negative.

The patient was diagnosed with brainstem encephalitis with positive GlyR-Abs. Follow-up Brain MRI in 3 and 6 months revealed progressive resolution of the lesion. (Figure 1: Panels a-d)

DISCUSSION

Glycine-Receptor is an inhibitory post-synaptic receptor, mainly distributed in the spinal cord, brainstem and cerebellum but also found in hippocampus, striatum and cortex. GlyR activity has been shown to control neurophysiological functions such as motor coordination, respiratory control, muscle tone, as well as pain processing.[1]

GlyR-Antibodies were first described in a patient with severe progressive encephalomyelitis with rigidity and myoclonus in 2008.[2] Since then in different case series the GlyR-Abs have been associated with two characteristic neurological syndromes, PERM and Stiff-Person-Syndrome.[3] Recently more clinical syndromes, such as brainstem encephalitis, epilepsy, acute disseminated encephalomyelitis with optic neuritis, optic neuritis and cognitive decline have been also described in patients with GlyR-Abs.[3,4] In about 10% of the patient with GlyR-Abs a tumor, such as thymoma or Hodgkin's lymphoma can be detected. Immunotherapy is the most common strategy to manage these patients, started with high-dose intravenous methyl-prednisolone, and followed by plasma exchange or intravenous immunoglobulin, or both. In first- and second-line therapy resistant cases other treatment such as cyclophosphamide or rituximab have also been used.[5,6]

Our patient presented with psychiatric disturbances, myalgia and epileptic seizure and during hospitalization he had episodes with painful spasms of upper-limb- and thorax-muscles. Radiological findings with a characteristic lesion in central pons and cerebral-peducles was a first trigger to think about pontine myelinolysis, without however electrolyte disturbances. After an extensive work-up GlyR-Abs were found positive only in serum and the clinical and radiological findings were attributed to an autoimmune encephalitis. The patient without specific treatment had a progressive clinical and radiological improvement. The titer of GlyR-Abs in serum remains at the same level six months later without detection of Abs in CSF. Almost one year after diagnosis the patient remains asymptomatic and the follow-up Brain-MRI shows a resolution of this lesion.

To the best of our knowledge this is the first published case with characteristic Brain-MRI-Images compatible with brainstem encephalitis and positive GlyR-Abs. This is as well the first case with spontaneous clinical and radiological remission. Our "watch and wait" therapeutic approach is unusual for patients with autoimmune encephalitis, since the majority receives early after the diagnosis immunotherapy. Further research would be meaningful, in order to specify in more detail the different phenotypes and the progress of the patients with encephalitis due to GlyR-Abs.

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